Schizophrenia Bulletin vol. 34 no. 6 pp. 1003–1005, 2008
doi:10.1093/schbul/sbn125
Advance Access publication on September 11, 2008

A Few Methodologic Issues of Note

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We have made progress in the past few decades in our understanding of psychiatric illnesses and identifying effective treatments. We can further this advancement by applying more stringent methods in our studies. In this editorial, I outline some of my favorite points of vexation in what I consider to be critical methodological shortfalls in studies of schizophrenia.

I will first consider an old favorite: negative symptoms. I think all authors of articles on schizophrenia agree that the avolitional pathology described by Kraepelin[1] is a core pathology affecting some, but not all, persons with schizophrenia. Parenthetically, the "not all" arises from present day emphasis on reality distortion symptoms as diagnostic criteria regardless of the presence of avolitional pathology. The negative symptom construct is broader than avolition and may be usefully dissected, eg, into restricted affect and reduced drive.[2,3] These primary negative symptoms are a direct expression of the disease process independent of reality distortion. It is also likely that all authors believe that secondary negative symptoms also occur. That is, negative symptoms with causes other than the direct pathophysiology of the illness. Common examples include anhedonia secondary to depression, diminished social engagement secondary to paranoia, constricted facial affect caused by antipsychotic drugs (ie, akinesia), and low interest and activity secondary to sedative side effects of therapeutic medication. Despite a seeming consensus on this issue,[2] most articles reporting negative symptoms use rating scales that do not distinguish between primary and secondary negative symptoms. And most of these report their findings without any mention of the primary/secondary negative symptom confound. This axe has been to the grinder on many previous occasions with only modest effect.[4–14]

Some studies address this confound with covariant analyses, but this results in unexplained variance that is not directly attributable to primary negative symptoms. This issue can be more decisively managed with a priori study methodology. The problem associated with secondary causes of negative symptoms has been highlighted in debates regarding efficacy of second-generation antipsychotic drugs for negative symptoms. A similar problem exists with studies reporting advantages in cognition. The advantages observed for negative symptoms and cognition are pseudospecific, to use a Food and Drug Administration (FDA) term. That is, the advantage may be explained by confounds rather than efficacy per se. Taking cognition for an example, a comparator drug such as haloperidol may slow processing speed, impede learning and reduce performance on cognitive tests resulting in the observed advantage for the second-generation drug.[15] Similarly, improved cognitive scores in a clinical trial during which psychosis improves may be secondary to clinical state changes that result in less interference with test taking. In negative symptoms, a drug that induces akinesia will look worse on restricted affect scores. Primary efficacy cannot be isolated in this circumstance, and statistical partialing out the effects of some potential confounds is not decisive. This is why a consensus has been developed on design requirements to address the pseudospecificity issue for cognition[16] and negative symptoms.[2] Representatives from the FDA participated in the development of the consensus on these designs clarifying methodology requirements essential in winning approval for a negative symptom or a cognition indication in schizophrenia.

Another methodological point is the status of schizophrenia as a diagnostic entity. Schizophrenia has the nosological status of a clinical syndrome rather than a validated single disease entity. Heterogeneity in clinical presentation and course is routinely observed, and heterogeneity of disease processes is likely. Nonetheless, most studies reported in the latter part of the 20th century studied schizophrenia as a disease entity without addressing heterogeneity. The result was vulnerability to false negative (type 2 error) findings and failures in replication based on cohort differences across studies. Advancing knowledge with hypothesis falsifying research is very difficult if the critical independent variables are not defined and assessed in the study cohort.[17,18] This has been an especially vexing issue in genetic studies where the analysis focuses on association with a syndrome class instead of a relevant phenotype. Fortunately, there is increased sensitivity to this issue, and National Institute of Mental Health is supporting major studies aimed at identifying key genotype/phenotype relations as a foundation for advancing knowledge on the genetic contributions to mental illness.[19,20] This approach will also help clarify which phenotypes are observed across present syndrome

classification boundaries and whether some are disease class specific.

There is now much interest in the overlap across diagnostic boundaries. There are 2 general problems with study designs approaching this question. First is the concept that a diagnostic class overlap exists based on a similarity that may represent an overlapping pathological dimension. Correlates of anxiety, for example, may be found in anxious persons in a number of diagnostic classes. This would support a hypothesis of similar anxiety processes across diagnostic boundaries but would not suggest that anxious persons with a diagnosis of schizophrenia, bipolar disorder, major depressive disorder, and social anxiety disorder belong to the same nosological class. The second problem is related. An author may use similarity observed across diagnostic classes to support the proposition that two *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition,* classes should be combined as one class. Whether the similarity is based on imaging data, genetic data, psychological data, or other dependent measures, the author needs to make a compelling case for why the measure is decisive for the classification issue. Correlates of fever will not support a case for similar disease class among infectious illnesses. Correlates of anxiety in the example above or, for that matter, reality distortion correlates across various psychotic illnesses may not be decisive for questions of diagnostic class. Most mental disorders have diagnostic criteria based on behaviors and subjective experiences that are on a continuum with the non-ill population, and many criteria are associated with multiple diagnostic classes and/or are experienced by patients in several diagnostic classes. The neural processes and genetic vulnerability for anxiety may be similar among persons experiencing anxiety without suggesting diagnostic unity. Hallucinations and delusions caused by lysergic acid diethylamide, amphetamine, temporal lobe epilepsy, bipolar disorder, delusional disorder, and schizophrenia may share correlates of final common pathways of expression without suggesting similarity of core pathology.

The literature related to similarities observed across diagnostic borders will be more clarifying when investigators make clear whether the variables relate to a dimension or to disease classification and, if the latter, to indicate why the correlated features are decisive for classification.

Even studies examining dimensions that span several nosological classes could be better refined in schizophrenia. Clinical trials testing efficacy for specific pathology are sometimes reported without methods for assuring that the subjects actually have the phenomena. For example, antidepressant therapy may be tested in schizophrenia subjects without requiring evidence of a major depressive episode. If a depression rating score is used as a selection criteria, there is no method reported for distinguishing demoralization, drug-induced dysphoria, or psychological reaction to loss from primary depressed mood. After 50 years of antidepressant drug therapy, the field still does not know the degree of its efficacy for a major mood episode in persons with schizophrenia.

These issues are relevant to the quality of scientific methodology for many studies involving schizophrenia. As such, they merit increased attention by investigators and by journal editors, referees, and readers.

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